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Characterization and Classification of External Quality Assessment Schemes (EQA) According to Objectives such as Evaluation of Method and Participant Bias and Standard Deviation

Discussion paper from the members of the External Quality Assessment (EQA) Working Group A[1]) on analytical goals in laboratory medicine

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Summary: Within the scope of this paper, the Working Group has attempted to place external quality assessment (EQA) within the whole context of quality management in laboratory medicine. First, the objectives of EQA schemes are defined and current EQA schemes evaluated. In most schemes, the objectives are not defined a priori and do not allow the definition of the origin of unacceptable individual results from participants.

There is an ongoing trend for making traditional EQA schemes more interesting for the participants. Analysis of the factors involved in analytical quality allow the definition of the essential analytical tasks of educational EQA schemes. Beside these quality control tasks, educational EQA also includes quality assurance elements.

EQA today has not only an important role to play in the assessment of each participant's performance but also in the assessment of the method. Efficiency of the schemes and educational impact can be improved by appropriate scheme designs according to objectives. After this theoretical approach, some practical examples of problem related EQA designs are given.

Introduction

Clinical laboratories have a long tradition of organisation and participation in external quality assessment (EQA) schemes. The first results in EQA schemes were reported by *Belk & Sunderman* (1) in 1947.

According to the ISO defintion, external quality assessment refers to a system of objectively checking laboratory results by means of an external agency, including comparison of a laboratory's result at intervals with those of other laboratories, the main objective being the establishment of trueness (2). This definition is rather static and does not include any educational aspect. Moreover, only participant assessment is considered, while method assessment is also an essential element of EQA.

Instead of external quality assessment, the term *"proficiency testing"* is also used for the same definition description (3). Proficiency testing is used rather in the scope of laboratory accreditation, allowing reimbursement based on results obtained in such schemes. In practice, the difference between proficiency testing and EQA is not always clear.

Recently, some organizers of EQA schemes have taken a broader view of the objectives of "traditional" EQA schemes (4, 5) and consider it an obligation to develop educational programmes that actively support quality improvements according to the needs of the laboratories.

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[1]) The Working Group is one of four ad hoc groups meeting under the auspices of the European external quality assessment (EQA) organizers group. The Working Groups were initiated by *Adam Uldall* following a meeting of EQA organizers and interested individuals in Cracow, Poland, in 1991 at Eurolab' 91.

[2]) Where *Dietmar Stöckl* presently is affiliated.

In these schemes, the emphasis changes from *assessing* the quality of analytical work to *assuring* quality by external guidance. *Olafsdottir* et al. (5) used the term: *"EQAssur"* as the most appropriate for such schemes. In this paper, we use the term "educational" EQA schemes. We could define educational EQA as problem related external quality assessment, allowing the participants to define the origin of problems for aberrant results and to find the appropriate remedial procedure.

Within the scope of this paper, the Working Group has attempted

(i) to place EQA within the whole context of quality management in laboratory medicine,

(ii) to define the objectives of EQA schemes,

(iii) to evaluate current EQA schemes,

(iv) to define the essential tasks of educational EQA schemes and

(v) to describe the design of educational EQA schemes according to the objectives.

Finally, some examples of problem related EQA designs are given, demonstrating the benefits of this approach, independent of the distinction made between EQA and proficiency testing. The Working Group restricted itself only to problems related to analytical quality. Consequently, areas such as preanalytical variation, test interpretation and organisational structure of a laboratory are not dealt with.

View of the Working Group

Situation of EQA within a total quality management concept

In the NORDKEM protein project publications, *Hyltoft Petersen* et al. (6) described in detail a model for analytical quality achievement (fig. 1). According to this model, at least three main elements are identified as the basis factors for analytical quality. These are

(i) *analytical quality specifications,*
(ii) *analytical quality creation* and
(iii) *analytical quality control.*

Within the model, EQA and internal quality control (IQC) are the two basic features of analytical quality control, each with a proper design and proper control materials.

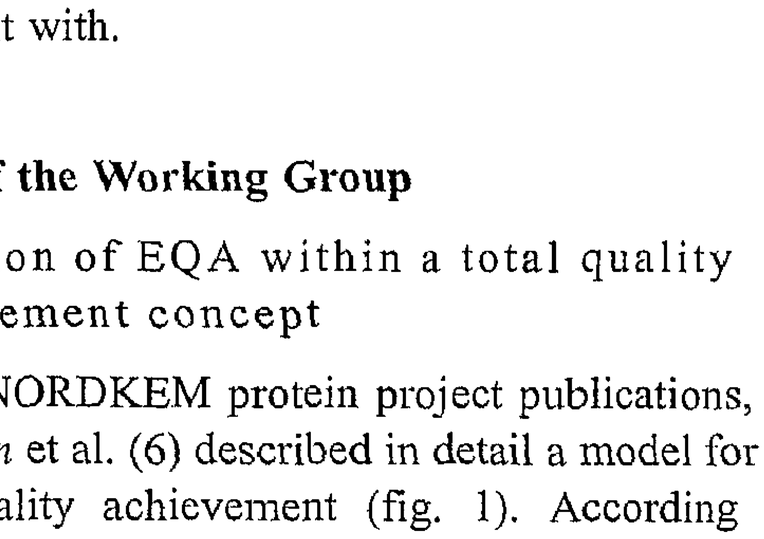


Fig. 1 Model for analytical quality illustrating the three basic elements as proposed by *Hyltoft Petersen* et al. (6).

In order to evaluate analytical quality, knowledge about the required performance of the analytical procedure is needed. That means that the desired analytical quality specifications have to be defined before any control procedure can be applied.

Analytical quality specifications

For internal quality control, analytical quality specifications are based on more or less complicated models with direct transformations of the more general goal to operative values for analytical bias and analytical imprecision. Both terms define the specifications for total error.

The quality specifications for an EQA result are given in terms of location and dispersion. Location is defined by the target setting, which can be method dependent or method independent. Depending on the scheme design, dispersion includes *random errors* and the *laboratory component of bias* or also *inherent bias of the measurement procedure.* For the definition of these error concepts, we refer to *Dybkaer* (7), who defines *laboratory bias* as the sum of the bias of the measurement procedure and the laboratory component of bias.

Our Working Group described in another publication (8) to pros and the cons of different quality specifications and proposed desirable routine analytical goals for quantities assayed in serum. In our opinion, the biological model is the most appropriate for EQA schemes, since this model is the most objective general approach. In some cases, e. g., therapeutic drug monitoring, phenylketonuria and thyroid stimulating hormone in neonatal screening tests, cholesterol and HbA_{1c}, acceptability limits for EQA results can be based on clinical concepts as, in these cases, the clinical use of these tests is well defined. The clinical concept relates directly to the clinical use of laboratory data, whereby, it is the most relevant approach to evaluation of analytical quality specifications. For most other situations, the laboratory does not know the exact clinical context in which the test result is asked; hence our proposal is to base acceptability limits, used in EQA schemes, on the biological model as a general approach, based on a general background of within- and between-subject biological variations without specifying the clinical situation.

The other analytical quality specifications, based on state of the art, on reference values or on expert opinions are discussed in the above mentioned paper from the Working Group. In figure 2, this extended model on analytical quality specifications is visualized.

Creation of quality

Creation of quality is, on the one hand, the responsibility of the diagnostic and equipment manufacturers (creation

of method quality) and, on the other hand, the responsibility of the individual laboratory (creation of laboratory quality). The quality demanded by the coherent set of desirable performance standards must be created, taking a number of factors into account. Lowering of imprecision can be achieved by use of better instrumentation and by the application of the techniques of quality assurance within laboratories. In contrast, improvement in bias can be achieved only by better standardisation through international reference preparations and calibrators with values traceable through the hierarchy of methods and materials and by use of more specific methods (9). This fact is of particular importance today, because bias is the major challenge for current method development (10). The European draft directive on in vitro diagnostics (11) also requires that standards and calibrators should be traceable to reference materials of a higher order.

Creation of method quality is mainly associated with thorough pre-market method validation. Each method should exhibit good sensitivity, specificity, precision, robustness and traceability. From all these characteristics, traceability to trueness is the most critical today. For a majority of clinical chemistry quantities, methods are calibrated by serum matrix calibrators and often by serum (multi)calibrators which are not included within the kit components. Consequently, traceability to trueness of a kit will depend on traceability of the calibrators used. Therefore, it is important that manufacturers recommend appropriate calibrators for each kit. Immunoassay kits normally include calibrators within each reagent package, hence the problem of the choice of recommended calibrators is irrelevant for most of these assay kits.

For those quantities where reference method values are available, traceability to trueness for calibrators and control sera should be performed, preferably by split-sample measurement with accuracy-based reference methods and routine method measurements on a representative panel of patient specimens (12). In this way, target setting of calibrators can be adjusted in order to compensate for non-commutability of their matrix and to guarantee trueness of patient sample measurements. This work must be performed by industry itself or in collaboration with reference laboratories. A proposal for a European Network of Reference Laboratories, with sufficient quality guarantees at the disposal of industry, has been elaborated within Workgroup B (13). When reference methods are not available, international reference preparations should be used for target value assignment. As an example we can mention here the BCR CRM for enzymes (14–16).

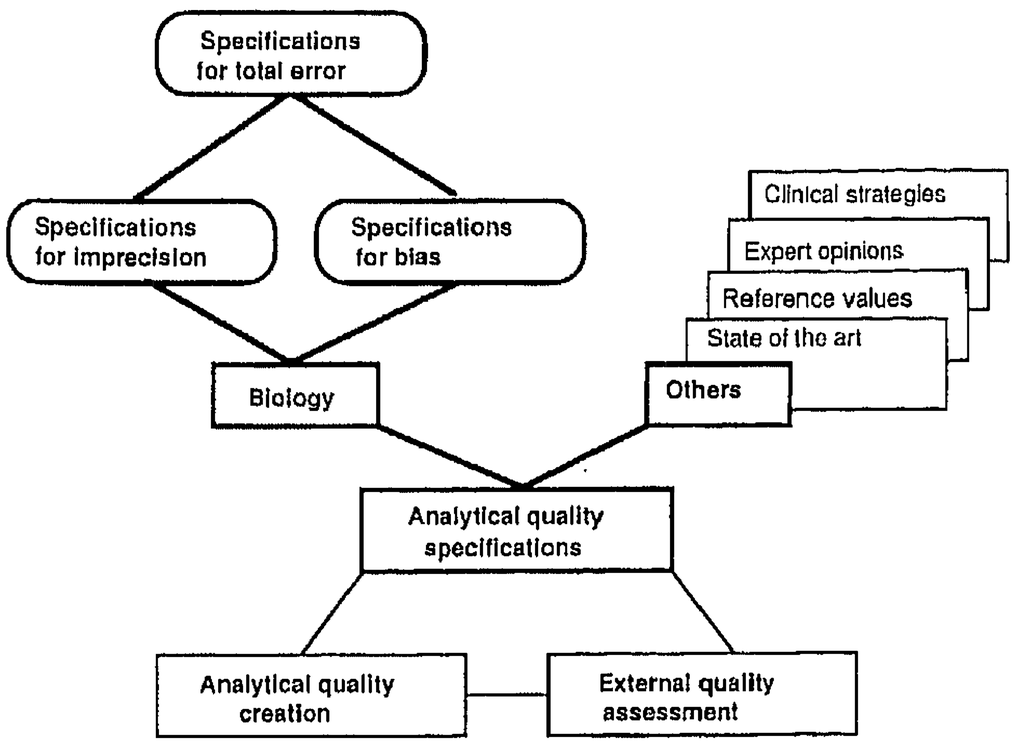


Fig. 2 Extended model for analytical quality specifications.

Creation of laboratory quality is associated with laboratory organization (adequate space, sufficient well trained staff, solid financial basis, efficient maintenance, etc.), adequate test-kit and instrument selection, and correct implementation of test-kits in combination with the recommended calibrator(s) and measurement instruments available in the laboratory. All these aspects can be summarized as "performance of procedures". Creation of laboratory quality as a function of the desired quality specifications requires that the laboratory applies constant working procedures and working instructions; this means that laboratories must use a method with an appropriate calibrator and measured on specific measurement equipment, in accordance with standard operating procedures. If this principle is not respected, there are no stable performance conditions and the set-up of adequate control procedures is impossible.

Many clinical laboratories are still not convinced that, even when they do not use a so-called closed method, they should make their own closed system (calibrator, kit, measurement equipment). Even if the performance conditions are stable, traceability to trueness can only be obtained if the manufacturer is more aware of traceability to trueness rather than to comparability of his results with those obtained with the kit/testsystem of a market leader for the same quantity. In this case, the method should be calibrated with the recommended calibrator(s) by the manufacturer. If this concept is not respected, all efforts from industry for traceability to trueness are worthless.

The concept of homogeneous methods must be promoted by EQA organizers by giving global results for the homogeneous method groups with sufficient users. Using EQA results, *Devleeschouwer* et al. (17) could demonstrate that traceability of C-reactive protein results for the same kit was much better for the users of the calibrator recommended by the manufacturer, as compared to the group using calibrators from other origins.

According to the expansions described above and focused on EQA, the model from figure 1 can be extended for the analytical quality creation element as illustrated in figure 3:

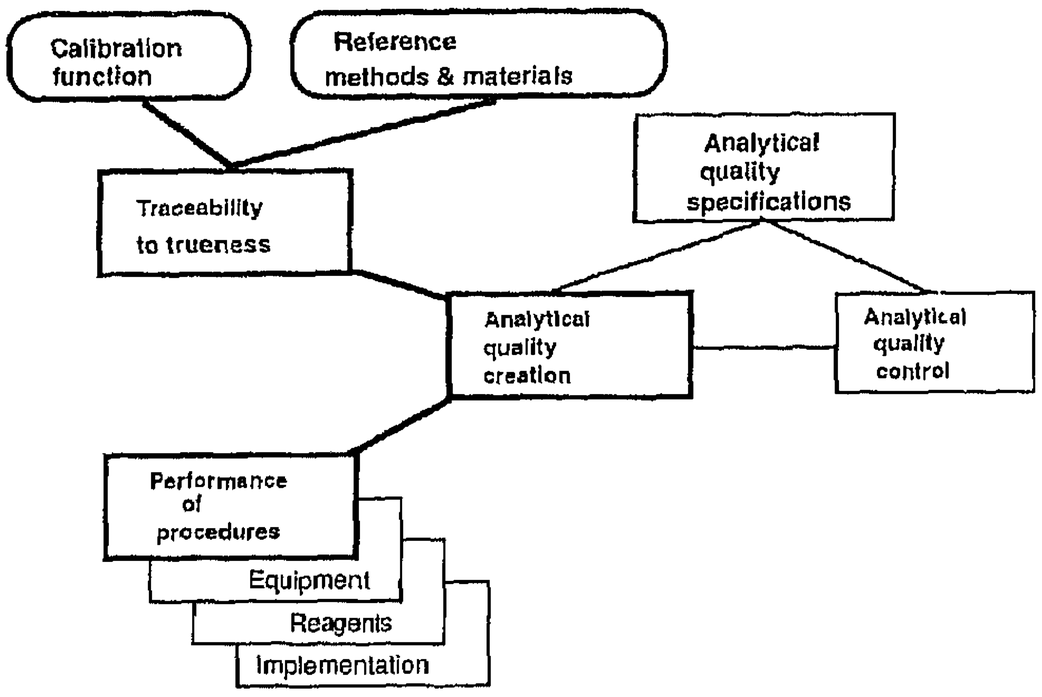


Fig. 3 Model for analytical quality, including the extensions for EQA.

Analytical quality control

In contrast to the generally accepted idea, *analytical quality control* cannot by itself improve the quality of an analytical process. Quality control by itself cannot create the desired quality, but primarily monitors it. Quality control processes can disclose or reject errors at best but the revelation of errors may be the first step in a trouble-shooting process which may lead to correction of the error, and thereby, to improvement in the analytical quality. It is important to distinguish between the possibilities for error detection by internal quality control and external quality assessment systems. EQA is no substitute for internal quality control, but complements it. The external system should disclose errors in the individual laboratory's stable performance, i. e. the chosen method with its calibration and implementation, whereas the internal control should disclose deviations from stable performance. Therefore, the external system is mainly a documentation of the stable situation and if the quality is unacceptable, then the method or the calibration should be changed. The external system thus deals with the stable analytical bias, but in some quality assessment schemes it also deals with documentation of random errors in order to assist the laboratories in their internal system. The fundamental strength of EQA is the large amount of data created, allowing conclusions to be drawn on sound statistical bases. The checking is necessarily retrospective and the comparison of a given laboratory's performance on a certain day with that of other laboratories cannot be notified to the laboratory until some time later. This comparison will therefore have no influence on the laboratory output on the day of the challenge. The objective of EQA is not to bring about day-to-day consistency but to give insight into between-laboratory comparability.

The design of the control system (both for IQC and EQA) will determine its ability to fulfill this purpose, since control materials as well as interpretation of the results are decisive for the outcome. The extended model for the analytical quality control is visualized in figure 4. The different EQA systems (proficiency testing, traditional and educational EQA) will be described further in this paper.

Recommendations for specifications of control materials, used in EQA schemes, have been prepared by Working Group C (18). Appropriate statistical evaluation procedures (which can be considered as belonging to the scheme design) and design of reports are under discussion in Working Group D.

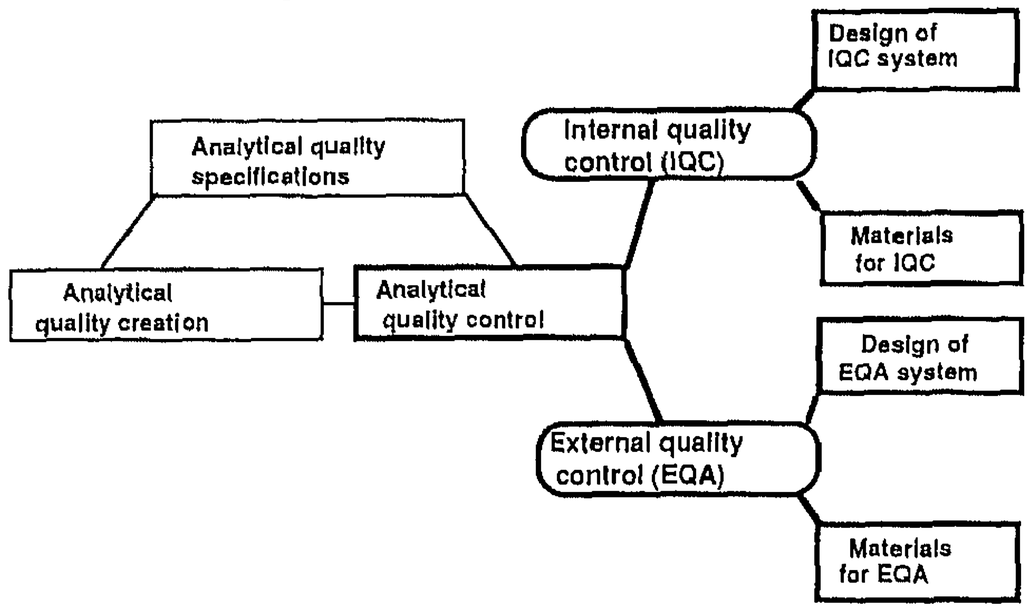


Fig. 4 The model for analytical quality from figure 1, illustrating the expansion of analytical quality control elements.

Objectives of EQA schemes

Based on the concept described above of quality management with analytical quality specifications, analytical quality creation and quality control, we can develop a similar model, describing the main elements of EQA (fig. 5).

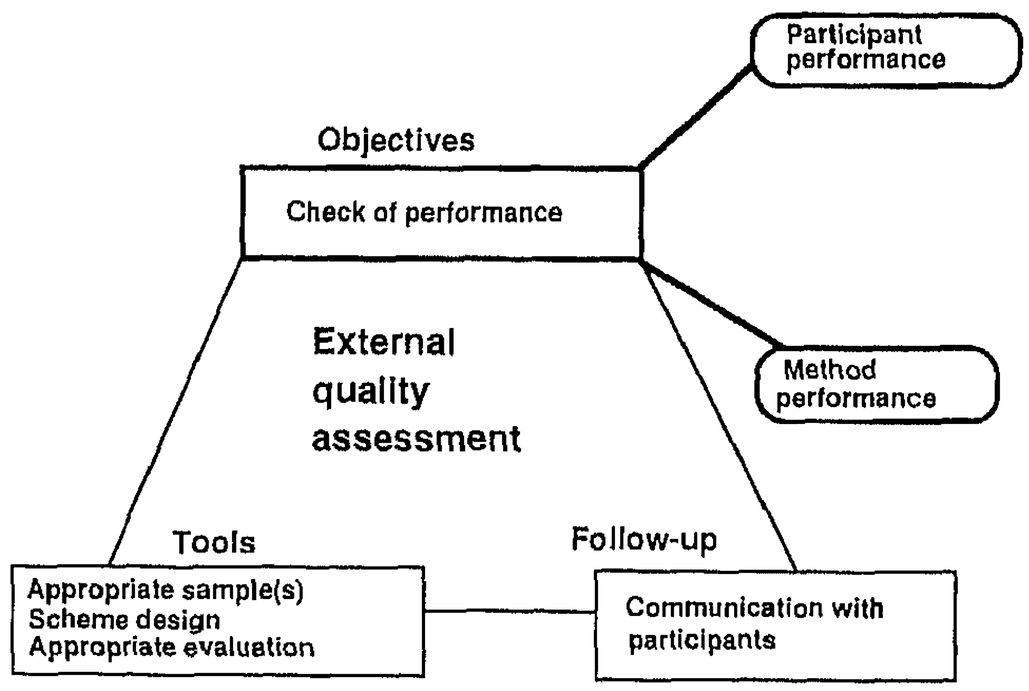


Fig. 5 Model for quality achievement applied to EQA.

In each EQA scheme, we can distinguish the following three basic elements:

(i) quality specifications (objectives),
(ii) tools and
(iii) follow-up.

The quality of an EQA scheme is obtained by linking these elements together. The objectives of EQA are of two types:

(i) participant performance evaluation and
(ii) method performance evaluation.

Creation of quality is defined by the tools. These tools are: appropriate samples, scheme design and an appropriate evaluation procedure in accordance with the objectives. Without defining the objectives, it is not possible to elaborate the tools and to inform the participants about the performances of the methods used and about the implementation. We can describe this concept as "problem related quality control".

Participant performance evaluation

Participant performance evaluation is related to the implementation of a method in a laboratory. The discussion within this paper is limited to the analytical aspects of the participant assessment. Other aspects of participant assessment such as: personnel, laboratory infrastructure, internal quality control, etc., are beyond the scope of this publication.

The primary aim of this evaluation is to assess the analytical quality of the individual laboratory in relation to other laboratories using the same methods and if possible, submitted to exactly the same external sources of quality.

Participant performance evaluation can be approached from two aspects; when is a result acceptable from a medical point of view (health policy objectives) or when is a result acceptable from a purely analytical viewpoint (analytical objectives)? As health policy objectives are also based on analytical performances in the long run, this theoretical split is not so clear in practice. Indeed, the performance evaluation will be based in both cases on analytical acceptable criteria, which can be different from each point of view.

The health policy objective of EQA is betterment of health care through improvement in laboratory performance. A national EQA programme can bring about such an improvement in two ways:

(i) by providing education, training and help for laboratories which require these or

(ii) by recognising laboratories with unsatisfactory performance (19, 20) and imposing sanctions on laboratories with persistent failures, thus effectively preventing them from contributing to the service.

Most European countries favour the first approach and most national EQA schemes put stress on education and training. Participation in such programmes can be mandatory or voluntary. Some countries, in addition, insist on bringing about a general improvement of laboratory standards by means of legal, financial or professional sanctions applied to laboratories which show poor performance. Legal sanctions may be applied to the denial of certificates of proficiency to the laboratories that are unable to reach defined standards of performance, and this in effect prevents them from practising. Financial sanctions may be similarly imposed: laboratories without a proficiency certificate may become ineligible to receive reimbursement from government or health insurance agencies for the investigations they perform. Professional sanctions may be applied by, for example, scientific societies or academies, in refusing to accord the status of recognised training centres to laboratories that do not participate in such schemes or show poor performance in them (21).

According to *Aronsson* et al. (22), international and regional EQA schemes can be used to assess one or more of the following aspects from the analytical objectives:

(i) the quality of the analytical performance of the individual participants laboratory;

(ii) the state of the art performance of the participating laboratories;

(iii) intra-laboratory variation;

(iv) inter-laboratory variation;

(v) relationships between calibration procedures and analytical results;

(vi) relationships between analytical procedure (proper) and analytical results;

(vii) relationships between commercial reagents and analytical results;

(viii) relationships between analytical instruments and analytical results;

(ix) state of the art values for concentrations of the constituents of the circulated material; and

(x) systematic deviations for the individual laboratory from state of the art values or values obtained by applying reference or definitive methods to the circulated material.

Some of these points overlap, but each represents a specific question put forward in connection with EQA. Efforts should be made to obtain information about most of the ten points in every EQA.

The Working Group suggests that the concepts of *Aronsson* et al. (22) should be expanded to include analytical quality specifications for participant and method performance evaluation.

Method performance evaluation

A method includes reagents, a calibrator and well defined measurement equipment. It is impossible to evaluate the reagents without considering the two other elements.

Method performance evaluation encompasses several aspects, such as: traceability, specificity, linearity, limit of detection, interferences, precision, etc. In fact, all these factors influence the quality of the result of a measurement. All analytical aspects of a method evaluation

should be investigated internally and comprehensively by the developer of the method before release on the market (see creation of quality). In this validation, traceability of calibrators is very important. Traceability is a task for industry, preferably supported by a network of reference laboratories. However, only few manufacturers are currently convinced that results obtained with their systems should be traceable to values based on recognised reference methods established either on the basis of split-sample patient samples or with the help of international reference preparations.

For the evaluation of method performances, a method independent target value, as far as possible traceable to trueness, is necessary.

EQA does not compete with the pre-market validation, but monitors the field performances and the ways in which methods are implemented in routine laboratories. It must also be mentioned that method assessment in EQA has not the same goal as the method assessment evaluation during the pre-market phase. In EQA, performance evaluation is often linked to the routine use of a method on well defined measurement equipment and a calibration system, which can be different from the reagent-calibrator-instrument combination used by the manufacturer during his validation process. Only EQA organizers have the information about which combinations of reagent-calibrator-instruments are used and must create homogeneous groups of users from the same method. For those groups with a sufficient number of users (same kit, same calibrator, same measurement equipment), an educational EQA scheme will evaluate the performance of these methods and the performances of each participant by comparing their results with those of other users of the same method. The importance of EQA as a post-market evaluation tool for industrially prepared kits and reagents is recognized in the European draft directive on in vitro diagnostics (11).

Critical evaluation of EQA systems

Under the general umbrella of the EQA system, we can distinguish:

(i) proficiency testing,
(ii) "traditional" EQA schemes and
(iii) "educational" EQA schemes.

The requirements on control materials and on evaluation procedures are similar for all the different types of EQA schemes; only scheme design and criteria for acceptable performance may vary.

Proficiency testing

Sanctions linked to inadequate performance are a distinctive characteristic of proficiency testing.

Successful participation for laboratory accreditation is required by several US Institutions such as the Health Care Financing Administration (HCFA regulations), Medicare, Medicaid, the Joint Commission on the Accreditation of Healthcare Organisations (JCAHO) and the College of American Pathologists (CAP).

To pass proficiency testing, clinical laboratories must meet desirable standards laid down under the Clinical Laboratory Improvement Act (32).

In Western Europe, the only EQA system classified as a proficiency testing programme exists in Germany and is conducted under legal constraintments laid down in the "Richtlinien der Bundesärztekammer" (RILIBÄK) (24). The merits of the German system are especially influenced by the fact that, in the original concept developed by *Stamm* (25), acceptability limits were based on reference values. This scheme uses reference method values as target values when reference methods are available (electrolytes, metabolites and substrates, steroid hormones, thyroxine and some therapeutic drugs). This is an unusual situation because the use of a single target is not the most appropriate for participant assessment. For all other quantities, where no reference methods or standardized methods are available, different method-dependent target values are used to evaluate the performance of participating laboratories.

Because of the possible sanctions, proficiency testing schemes have to respect current analytical performance and, hence, are often restricted in the limits they choose and the nature of targets they apply. For example, the German EQA limits for some steroid hormones had to be widened when method dependent target values were substituted with reference method target values (26) because, currently, calibration and/or specificity of test-kits from different manufacturers is not compatible.

Because of the possible sanctions, proficiency testing schemes have to take extreme care that laboratory performance is not confounded by method performance (9). As an example, it is impossible in a proficiency testing scheme to include samples that contain interferents in order to assess method specificity (27, 28). In a pure proficiency testing scheme, participant assessment must be independent from the measurement procedure used, because a user cannot be blamed for shortcomings of the method itself (he can only be blamed for using a method with poor performances). Therefore, CAP uses a protocol to compensate for the bias of the measurements procedure, based on the simultaneous determination of fresh human sera and CAP survey specimens (29).

It could be presumed that the basic quality specifications should be the same for regulatory (licensing, accreditation) purposes in different countries. However, large differences are observed in the applied acceptability limits. For the same results for the same quality, the laboratory would fail proficiency testing in one country but would pass in another and vice-versa (30).

The rationale behind the different limits is not always clear and is based on different quality specifications. Finally, proficiency testing schemes might not mirror true laboratory performance because of tendencies to use special practices for EQA samples (31) in order to pass a survey. In fact, a participant cannot afford the smallest risk of loosing their certification (license).

In conclusion, it can be stated that pure proficiency testing schemes have recognized major limitations. In spite of the intentions of protecting against unprofessional performance, proficiency testing has a tendency to maintain the quality at a certain level and is unable to stimulate improvement of quality above this level.

Traditional EQA schemes

A review of European EQA schemes was published by Measurement & Testing from the EU (32). Moreover, other authors have extensively reviewed EQA schemes in all the disciplines of clinical pathology (4, 33–35). In most European countries, EQA schemes belong to the category of traditional schemes.

EQA will only reflect routine quality if all users are allowed to treat the EQA samples in the same way as usual patient samples, even with the risk of making a mistake. Since no sanctions are linked to poor EQA results, there is a greater chance that a traditional EQA (with essential educational purposes) will give a more realistic reflection of the routine quality of a laboratory than proficiency testing schemes. In contrast to proficiency testing, more stringent acceptability limits can be used in EQA.

The VALTECH ("Commision: validation des techniques) criteria (36) in France and the Combi-scheme in The Netherlands (37), for instance, both based on biological variation, are used for drawing the attention of laboratories to their current quality and for promoting higher quality methods. In constrast to proficiency testing, EQA schemes can introduce experimental samples for which it is known that a majority of the participants will fail, but with an important educational impact and particularly when the results are discussed in detail in the comments on the survey. Such surveys cannot be organized in proficiency testing.

In some countries, such as Belgium, Luxembourg, France and several Eastern Europe countries, participation in EQA schemes is mandatory. These schemes remain educational and cannot be linkened to proficiency testing schemes as there are no sanctions directly coupled to laboratory performances in EQA. Mandatory participation, as foreseen in the countries mentioned, will force these laboratories to participate, which would not be the case in a completely free system. Therefore, participation in the official EQA schemes is included in the licence conditions in Belgium and France; in these countries EQA is organized by governmental organisations.

In a majority of the countries, participation in EQA schemes is completely voluntary and national or regional EQA schemes are organized by professional or scientific societies and by non-profit organisations.

In addition to "official" EQA schemes, it must be mentioned here that there are several commercial EQA schemes often coupled to the purchase of control materials. These schemes are often linked to a well-defined group of users of the same method.

Acceptable performance criteria in European EQA schemes were reviewed in another paper by our Working Group (38) and by *Libeer* (4).

Traditional EQA schemes normally send out two samples per survey. Participants are asked to perform a single determination on each sample. Results are usually grouped according to method groups. Since a result is not only influenced by the analytical principle, but also by the reagent, calibrator and measurement equipment, it is sometimes extremely difficult to create homogeneous participant groups with a representative number of participants. Most traditional EQA schemes do not have all of this information at the moment.

As a consequence of the single determination, it is difficult to assess laboratory performance in terms of bias and random errors.

Several traditional EQA schemes give a review of the group performances for each sample. In clinical chemistry however, many incorrect conclusions might be drawn from such evaluations, because all the groups do not cover the same contents: some groups cover only the same analytical principle (e. g. glucose hexokinase methods, covering different kits and instruments); other groups cover a well-defined method (e. g. glucose reflectometry, covering only Johnson & Johnson slides on Ektachem).

Educational EQA schemes

In Europe, an increased awareness of the deficiencies and the shortcomings of the design of most current "traditional" EQA schemes is growing. Some of these criticisms were already mentioned under proficiency testing and traditional EQA. Educational EQA tries to improve traditional EQA (and the inherent shortcomings) and to add a new scope, emphasizing quality improvement.

As a consequence of this new approach, the following elements are to be considered:

(i) assessment of the overall analytical quality, including long-term follow-up

(ii) conducting specialized EQA schemes, where specific analytical pitfalls are studied

(iii) assessment of quality improvement

(iv) supporting internal quality control continuously by specially designed EQA schemes

(v) monitoring the methods and the laboratory performance through a simplified EQA scheme using detailed information about methods

(vi) stimulating proper action taken by the laboratory when deviating findings occur

(vii) promoting of the use of common reference intervals where relevant and the use of modern nomenclature and units in collaboration with other interested professionals or societies.

As observed, the scope of an educational EQA scheme is much larger than traditional schemes and quality assurance elements are also included.

We could define educational EQA or external quality assurance as problem related external quality assessment, allowing the participants to define the origin of problems for aberrant results and to find the appropriate remediation procedure. Therefore, analysis of the data returned to laboratories by the organizers of EQA schemes must be improved so that poor performance can be properly highlighted, the reasons for the poor performance made readily apparent to all involved in laboratory medicine, and educational advice for trouble-shooting provided if required (39).

The Working Group stresses that the design of an educational EQA scheme should always bear in mind which objective it desires to address. The EQA design should reflect this **before** sending out the samples, rather than try to extract the data afterwards, for example, bias data from a survey that primarily was intended for investigation of method CV. This approach will affect selection of the sample type (e. g. native or processed and lyophilized), the number of measurements to be performed by the individual laboratory (single or multiple), the type of target (group-mean, consensus, reference method), data grouping (built-up of homogeneous groups with respect to method, manufacturer of reagents, instrument, etc.), number of surveys conducted per year.

Control specimens distributed in EQA schemes must be carefully designed to provide correct information and be appropriate for the intended objective (40).

For example, single target setting is inappropriate for participant assessment, while multiple target setting is inappropriate for method assessment (9) and jeopardizes efforts for method harmonisation (20). Bias assessment of methods needs native sera, while processed, lyophilized materials are mostly inappropriate for that purpose because of "matrix effects" leading to non-commutability with patient specimens (41). Examples of EQA designs according to analytical quality specifications, given in the appendix, demonstrate how traditional EQA schemes could evolute to educational EQA schemes by a problem related approach for the organisation of the schemes, according to objectives set a priori.

In order to schematize these various possibilities, the Working Group first classified the analytical factors, which are principally factors involved in analytical quality. We made a main distinction between "external factors" (factors associated with the method assessment) and "internal factors" (factors associated with the laboratory implementation) and between "permanent" and "variable" factors (see tab. 1).

Classification of relevant factors involved in analytical quality

A schematic presentation of the relevant factors involved in analytical quality is given in table 1.

The *permanent external factors* are related to the laboratory's choice of the analytical principle, the equipment, the calibrator and kit-reagents, etc. This can only be modified by selecting another (better) analytical system. The individual laboratory has little influence on the quality of these products. The impact of these factors on EQA will result in

(i) deviating values (from a true value) for all laboratories using the same method or kit and (or)

(ii) in inferior imprecision performance (elevated method group CV).

In the first case, the producer has to review the choice of basis for calibration and for the traceability back to

Tab. 1 Factors involved in analytical quality

Sources	External factors	Internal factors	
Permanent factors	Analytical principle, Method, Equipment	Implementation in the laboratory, Instructions	*Laboratory's choice of quality*
Variable factors	Variation in batches	Variation in performance and regular errors	*Expected and unexpected variation*
	Manufacturer's responsibility	*Laboratory's responsibility*	

this (situation where EQA samples were proved to be commutable); in the second case the method is to be considered as poor because of the inherently poor methodological principle or because the implementation of the analytical principle as it is worked out in the method or in the measurement equipment is bad. These systems should be abandoned.

The Working Group considers that the permanent external factors do not need to be assessed more than once a year, but carefully investigated and measured during several days.

The *permanent internal factors* are related to the implementation of the method in the laboratory (reagent/sample volumes, commercial calibrators, the number of calibration points, curve fittings, calculation factors, time factors, etc.). As an example, albumin determination with bromocresol green is usually treated by a linear function, although a logarithmic function is more appropriate. Further, the time factors chosen may result in different sensitivity for non-specific reactions, e. g. in the *Jaffe* creatinine determination. The influence of acetoacetate on the *Jaffe* creatinine determination can be neglected if incubation time before the first reading is at least 60 seconds (28). These problems are highlighted in EQA by systematic deviation from the method group mean (median) for individual laboratories within the same user group.

Permanent internal factors must be controlled during verification of the implementation of the method in the laboratory and in practice also once a year, so that the current 'permanent' situation is kept up to-date.

For this control, materials with known values are needed. These materials should be available to the users by the manufacturers, when new methods are introduced or when difficulties arise. These materials could also be included in EQA and made available by EQA organizations.

The *variable external factors* are due to variations in batch production (both calibrators and reagents). This can best be controlled when new batches are compared to old batches by selected laboratories, before they are released for all laboratories, and by the individual laboratory when using a new batch. Another course of action would be to obtain from the producers a better warranty for closer batch to batch variations and to advise laboratories to use the same reagent and calibrator batches over a long period.

As EQA surveys are organized in fixed schedules, it is practically impossible to control these factors in an EQA. On the contrary, laboratories should be aware of this problem and increase internal control procedures when batches are changed.

The *variable internal factors* must be controlled

(i) by the laboratory internal quality control system in each run and

(ii) in the external quality assessment by evaluation of random deviations from the method group mean (median) for individual laboratories.

For an evaluation of variable internal factors, it will be necessary that participants perform multiple measurements in several series.

In table 2, the most relevant characteristics of each of the described factors responsible for analytical quality are mentioned.

Essential tasks of educational EQA schemes

Existing EQA schemes include less or more elements of educational EQA schemes and in practice there is not such a clear distinction between the two. In a traditional EQA approach, a survey is run and afterwards the organizer tries to draw conclusions. Educational EQA schemes are more structured from the beginning: the objectives are well defined and the concept planned beforehand. Within educational EQA schemes, we distinguish the following essential tasks:

(i) Monitoring and
(ii) evaluation of relevant quality factors.

Monitoring

Monitoring does not evaluate individual EQA results of participants; only pure assessment is considered here without any reference to quality specifications. As an example we can mention the state of the art performance of a participant group, long-term follow up of this performance, comparison of the performance from one participant group (country) with another, performance comparison of different analytical principles.

This information is important for the demonstration of the quality of clinical laboratories in general.

Tab. 2 Most relevant characteristics of factors involved in analytical quality

Permanent factors	Traceability	Calibration function
	Linearity	Systematic error
	Interference	Carry-over
	Specificity	Contamination
	Detection limit	Conformance to consensus value
	Precision profile	Utensils
	Instrument variability	
	Commutability of control materials	
	Carry-over	
Variable factors	Batch variability	Within-run imprecision
	Stability of reagents, calibrators	Within-day imprecision
		Between-run imprecision
		Between-day imprecision
		Long term performance

Evaluation of quality factors

Knowledge of the relevant factors involved in analytical quality allows the design of educational EQA schemes to be focused on the problems one by one.

EQA can be used for the investigation of all factors involved in analytical quality as resumed in table 2. However, EQA is not always the most appropriate tool to be used for every item to be investigated.

Table 3 gives a review of which factors should best be investigated by internal quality control procedures and those which are appropriate for EQA schemes. Examination of the factors involved in analytical quality allows the definition of the essential tasks for educational EQA schemes.

Examples of problem oriented designs of educational EQA schemes are given in the appendix.

Within the evaluation of permanent external factors, traceability is one of the most important.

If the concept of a network of independent reference laboratories is widely accepted by the manufacturers and if all results on traceability of methods are available for EQA organizers and for the users, then it is supposed that this type of verification should be done only once a year. EQA has a major task to demonstrate bias of methods and, together with the users, to stimulate manufacturers to provide more accurate methods.

For this assessment, it is sufficient that only a representative number of participants from a homogeneous group assay the samples. Indeed, it would be a waste of resources to try to generate homogeneous groups **after** performing a survey. This approach presumes that the EQA organizer has knowledge, not only from the analytical principle groups to which the participants belong, but also from the reagent, calibrator and measurement equipment in use from each participant. A practical example of such a survey is published by *Stöckl* et al. (42).

The requirements for appropriate control sera for method performance evaluation are high, namely certified fresh native sera in several concentration ranges. A preliminary selection of participants allows the needed information to be gathered in a much more economical way. This approach does not mean that the information must only be available to the participating laboratories, but it is also important that the evaluation report should be communicated to all the scheme members.

By using dedicated designs and samples, EQA can be used for studying robustness of methods, sensitivity to interferences, linearity, recovery, specificity and other permanent factors. Several examples of such studies can be found in the UK steroid hormones NEQAS (43).

For these evaluations, if only a limited number of participants are asked to collaborate, a practical problem arises: in most countries laboratories have to pay a fee for their participation in the EQA programmes. Some participants could argue that they do not want to pay for the performance evaluation of a method, but only for their own performance evaluation. To avoid this situation, each survey concept on method performance evaluation should also try to give maximum information on the performances of the individual participant.

Batch variability of reagents and calibrators can best be controlled by IQC procedures. When changing batches of reagents or calibrators, laboratories should increase their internal control procedures.

If a sufficient number of users of the same batches are found, in EQA it is possible to compare the performances of different batchnumbers for calibrators and methods.

This assessment aims at the verification of the correct implementation of a method within the laboratory (including calibration function and the setting up and working out of the performance). Correct implementation will result in an acceptable laboratory component of bias. The impact of the laboratory component of bias can only be evaluated if the bias of the measurement procedure elements (belonging to the external permanent factors) are eliminated. The laboratory component of bias is defined as the difference between the group mean value of the users of a same method and the inter-run laboratory mean (7).

According to the problem related control approach, educational EQA must give an answer to the participant if performance is sufficient to meet to the assumed quality specifications. If this is not the case, maximum information must be given in order to disclose the problems.

In a previous paper on desirable analytical performance standards (8), the Working Group recommended that quality specifications should be based on biology. These desirable analytical performance standards must then be specified in terms of maximum allowable bias and imprecision for monitoring and for diagnostic testing.

Tab. 3 Essential quality functions for IQC and EQA related to the factors involved in analytical quality

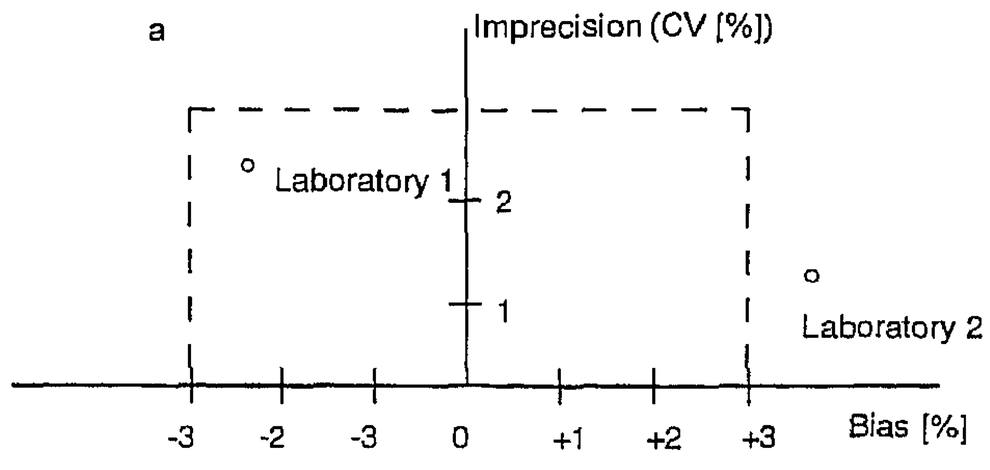
Sources	External factors	Internal factors
Permanent performance	External quality assessment	External quality assessment
Variable performance	Internal quality control (External quality assessment)	Internal quality control
	Kit/test system performance	Participant performance

When achieved, these performance standards should guarantee optimum patient care.

Often a participant is not able to improve the inherent bias of the analytical principle and the traceability of the method used. The laboratory component of bias can be evaluated by comparing the mean of multiple determinations (grand mean) from one laboratory versus a consensus value (mean or median). The difference between the consensus value and the reference method value cannot be considered as an estimation of the bias of the measurement procedure if commutability of the control samples has not been investigated. A method for commutability evaluation of control sera was described by *Malavasi* et al. (44) and *Baadenhuijsen* et al. (45).

Maximum allowable bias and imprecision for meeting the assumed quality specifications can be evaluated separately or by combining the different components: bias of the measurement procedure, laboratory component of bias and random errors.

For cholesterol, the national cholesterol education programme (NCEP) Laboratory Standardisation Panel (46) goal guidelines state that inaccuracy is acceptable if the bias is $< \pm 3\%$ and CV $\leq 3\%$. If for other quantities, the goal shares common reference intervals, then the acceptable performance will take into account both aspects. The examples for cholesterol and for plasma proteins are shown in figure 6.



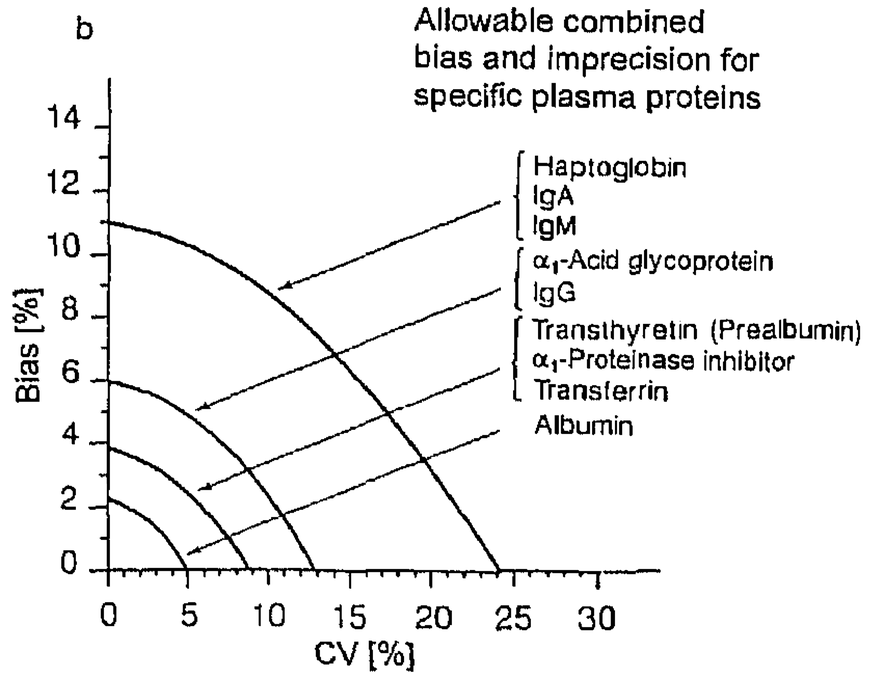


Fig. 6 Acceptability limits for bias and imprecision.
a: is the example for cholesterol where bias and imprecision are considered independently: Lab 1 conforms to both specifications, Lab 2 conforms to the specifications for imprecision but the bias is too large.
b: is an example of the combined bias and imprecision as used in the Nordkem protein project for specific plasma proteins (49) (reproduced with permission).

Since the acceptable bias is a combination of the laboratory component of bias and bias of the measurement procedure, the maximum allowable laboratory component of bias will depend on the bias already taken up by the manufacturer for the method itself. A discussion about the maximum allowable bias of the measurement procedure for each quantity between all involved parties (industry, EQA organizers, professionals) would be useful.

Quality assurance tasks

The educational role of EQA schemes is very important. Quality of a laboratory result does not stop with a correct analytical result. Also, EQA can be helpful in data interpretation by collecting other information from participants and by appropriate evaluation of these data. Examples include:

– EQA schemes can ask that protein results are calibrated against the new worldwide available CRM 470 so that results between laboratories are more coherent.

– Appropriateness of reference intervals used. Examples are found in the Danish EQA scheme for specific proteins (47).

– Correct interpretation of results. The Murex immunoassay scheme has considerable success in this field.

– Support of internal quality control. According to the design of the schemes, participants are asked to perform one or several measurements. Multiple measurements can be used for the evaluation of laboratory imprecision.

– To provide educational assistance and education. The laboratory Proficiency Testing Program in Toronto (Canada) even has a teleconference programme for interactive education (48).

Appendix

Table 4 lists problem related EQA designs for method evaluation with their essential prerequisites. Practical examples for participant evaluation and for method evaluation are elaborated further in the following examples.

1. Examples of EQA schemes for participant performance evaluation

Frequency:

3–12 times/year, according to the needs and the practicability within the EQA scheme.

Tab. 4 Problem oriented designs: examples of essential prerequisites

Investigation	Sample nature	Target setting
Measurement procedures bias	Native human serum	Reference method value
Laboratory component of bias	Native human serum	Method group mean and reference method value
Within-method CV (between laboratories)	Any stable material	No target value
Method specificity and interferences	Two identical sera with/without added substances	No target value
Laboratory systematic deviation	Any stable material	Method group mean

Needed information:

Reagents (Manufacturer, analytical principle, possibly batchnumber).

Calibrators (manufacturer, type, possibly batchnumber).

Measurement instrument (manufacturer, type).

Prerequisites:

Processed samples.

Target being the mean (median) of a homogeneous group (same analytical principle, same reagent, same reagent with same calibrator(s), same reagent with same calibrator(s) on the same type of measurement instrument, etc.).

Statistically sufficient number of participants of a homogeneous group.

Statistically sufficient number of measurements performed under stated conditions.

EQA scheme design 1:

2 samples/event and 1 measurement/sample (giving two data points/participant).

Conclusions to be drawn:

Basic information on the use of different methods, allowing identification of the users of a homogeneous group.

Estimation of the state of the art performance based on the overall method mean (median) and in the method groups with sufficient users.

The deviation of the individual result from the group target is composed of imprecision and bias components.

No estimation of the laboratory component of bias.

No estimation of the intra-laboratory reproducibility.

No estimation of the bias of the method.

EQA scheme design 2:

2 samples/event and 6 measurements/sample: duplicates on 3 days (giving 12 data points/participant).

Conclusions to be drawn:

Basic information on the use of different methods, allowing identification of the users of a homogeneous group.

Estimation of the state of the art performance based on the overall method mean (median) and in the method groups with sufficient users.

Estimation of the laboratory component of bias in these homogeneous groups with sufficient users.

Estimation of the intra-laboratory reproducibility.

No estimation of the method bias (even if a reference method value is available, the method bias can be erroneous due to possible lack of material commutability).

Design 2 gives better estimation of deviation and allows calculation of reproducibility, but creates more data to process and imposes a higher workload on a participant.

2. Examples of EQA schemes for method performance evaluation

Frequency:

Once a year, or after the introduction of new kits or methods with sufficient number of participants.

Needed information:

Reagents (manufacturer, analytical principle, possibly batchnumber).

Calibrators (manufacturer, type, possibly batchnumber).

Measurement instrument (manufacturer, type).

Prerequisites:

Native serum samples.

Target being a conventional true value (ID-GC/MS reference method value).

Statistically sufficient number of participants of a homogeneous group.

Statistically sufficient number of measurements performed under stated conditions.

EQA scheme design 1:

Four frozen native serum samples, "single donations".

Homogeneous group of 20 laboratories; 6 measurements/sample: duplicates on 3 days (giving 120 data points/sample).

Conclusions to be drawn:

Estimation of the method bias.

Estimation of the inherent reproducibility of the method.

Estimation of the laboratory component of bias

Estimation of the intra-laboratory reproducibility

EQA scheme design 2:

Four frozen native serum samples, "single donations".

Homogeneous group of 40 laboratories; 1 measurements/sample: (giving 40 data points/sample).

Conclusions to be drawn:

Estimation of the method bias.

Estimation of the inherent reproducibility of the method.

No estimation of the laboratory component of bias.

No estimation of the intra-laboratory reproducibility.

Both designs give information additional to the primary objective.

Design 1 has reduced shipping costs and gives more information for the individual participant, but creates more data to process and imposes a higher workload on a participant. Design 2 requires more participants. Consequently, it will take a longer time before a new method can be evaluated.

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